REMARKS

Status of the Claims

Claims 1-20, 25-27, 29-40, and 43-57 are pending. Claims 29-30, 43-44, and 46-49 have been withdrawn from further consideration by the Examiner as being directed to a non-elected invention. Claims 1-20, 25-27, 31-40, 45, and 50-57 are currently under consideration.

The Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-20, 25-27, 31-40, 45, and 50-57 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification as-filed. Specifically, the Examiner alleges that the specification enables only the use of PSGL-1 and fragments thereof for inhibiting P-selectin and its activities. The Examiner therefore contends that the specification does not enable the use of PSGL-1 and fragments thereof for "binding to," "interacting with," or "modulating" P-selectin and its activities. The Examiner also notes that "binding," "interacting," or "modulating" to P-selectin need not necessarily encompass inhibiting P-selectin and its activities, because such terms may read on agonistic or antagonistic activities. In addition, the Examiner further alleges that the specification enables only the use of PSGL-1 and fragments thereof to inhibit P-selectin and its activities in specific cell types (*e.g.,* leukocytes or platelets), and does not enable their use to inhibit cellular adhesion, cell migration, or movement of cells generally.

Without acquiescing to these rejections, and solely in an effort to further prosecution, Applicants have amended the claims to recite specific inhibitory activities and cell types, as suggested by the Examiner. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Rejection Under 35 U.S.C. § 102(e)

Claims 1-4, 8-13, 16-18, 25-27, 45-47, 50-53, and 57 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 5,464,788, issued to Cummings *et al.* ("Cummings"), and as further evidenced by The Merck Manual of Diagnosis and Therapy ("The Merck Manual"). Cummings teaches the use of PSGL-1 in the treatment of acute and chronic conditions associated with leukocyte adherence, inflammation and coagulation, including ischemia-reperfusion injury, atherosclerosis, and stroke. The Merck Manual teaches simply that arterial hypertension is a complication of atherosclerosis, cerebrovascular insufficiency associated with stroke, and renal failure. THE MERCK MANUAL OF DIAGNOSIS AND THERAPY 1417-24, 1632, 1654-58 (17th ed.).

The Examiner acknowledges that Cummings is silent about hypertension, but maintains the instant rejection because Cummings teaches treatment of conditions and diseases associated with hypertension. The Examiner continues to allege that persistently high arterial blood pressure or hypertension associated with the various acute and chronic conditions disclosed in Cummings would have been inherently inhibited or treated by the administration of inhibitory PSGL-1 and fragments thereof as taught by Cummings. (3/17/05 Office Action, pg. 4). Further, the Examiner alleges that the functional limitations claimed in the instant

application would have been inherent properties of the methods of treating ischemia-reperfusion injury, atherosclerosis and stroke taught by Cummings.

To serve as an anticipation reference in an inherency rejection, the reference must make clear that the missing descriptive matter is necessarily present in the thing described in the reference. *Schering Corporation v. Geneva Pharmaceuticals, Inc.,* 339 F.3d 1373, 1376 (Fed. Cir. 2003) (emphasis added). In relying upon the theory of inherency, the examiner bears the burden to "provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original); MPEP § 2112 (8th ed., 2nd revision, May, 2004). The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993); MPEP § 2112. Applicants respectfully assert that the Examiner has failed to meet this initial burden.

First, the teachings in The Merck Manual make it clear that not all patients with stroke or atherosclerosis suffer from hypertension. The section on stroke indicates that while strokes may be caused by hypertension, they may also be caused by numerous other problems not associated with hypertension, such as hemorrhage due to congenital aneurysm, arteriovenus malformation, and embolism (air bubble in the blood). *See* THE MERCK MANUAL, pages 1417 and 1421. Additionally, hypertension is not caused by stroke, and it is not listed as a

symptom or sign of ischemic strokes or transient ischemic attacks. *Id.* at 1420-1421. Instead, symptoms of stroke include aphasia (loss or impairment of the power to use or comprehend words), hemiplegia (total or partial paralysis of one side of the body), hemianesthesia (loss of sensation in either lateral half of the body), hemi-sensory loss, and confusion, etc., depending on the location of the stroke.

Similarly, the discussion of atherosclerosis in The Merck Manual clearly shows that, although hypertension is one of many risk factors for atherosclerosis (*i.e.*, patients with hypertension may develop atherosclerosis), there are other unrelated causes of atherosclerosis, such as serum lipid levels, high levels of blood homocysteine, and *C. pneumoniae* infection. *Id.* at 1656-57. Furthermore, hypertension is notably not included in the symptom section of atherosclerosis. Instead, The Merck Manual states that "[a]therosclerosis is characteristically silent until critical stenosis, thrombosis, aneurysm, or embolus supervenes." *Id.* at 1657. Therefore, patients with atherosclerosis do not necessarily have or develop hypertension.

The issue is not whether patients with hypertension also have atherosclerosis or strokes, but whether patients with atherosclerosis or strokes necessarily have hypertension. The fact that patients with hypertension may later develop atherosclerosis or be at increased risk for suffering a stroke does not show that patients with those conditions necessarily have hypertension. The discussion of the causes of hypertension in The Merck Manual confirms this view—neither atherosclerosis nor stroke are listed as a cause of hypertension.

Id. at 1420-21, 1656-57. Merely because some patients with hypertension develop one of the two conditions listed in Cummings does not mean that all of the patients in Cummings with either of those conditions necessarily also have hypertension.

Finally, Applicants note that the specification discusses the utility of the invention in treating patients with hypertension and thrombosis, or those with hypertension who are also at risk of thrombosis. As hypertension does not necessarily result in thrombosis, even if the patients in Cummings had hypertension (which Applicants believe was not necessarily the case), that reference does not teach that the patients also had, or were at risk for, thrombosis. Thrombosis is not inherent in hypertension, because patients with hypertension do not necessarily have thrombosis. Therefore, Cummings cannot inherently anticipate the claimed invention as it does not teach or suggest treatment of patients with hypertension. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Rejections Under 35 U.S.C. § 103(a)

A. Cummings and Larsen in view of Blann, Araneo, DeFrees and The Merck Manual

Claims 1-20, 25-27, 31-40, 45, and 50-57 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Cummings and U.S. Patent No. 5,840,679, issued to Larsen *et al.* ("Larsen"), in view of Blann et al., *J. Hum. Hypertens.*, 11(9):607-609 (1997) ("Blann"), U.S. Patent No. 6,150,348, issued to

Araneo *et al.* ("Araneo"), U.S. Patent No. 5,604,207, issued to DeFrees *et al.* ("DeFrees"), and further in view of The Merck Manual.

The Examiner acknowledges that neither Cummings nor Larsen discloses inhibition of hypertension and deep vein thrombosis by inhibiting P-selectin and PSGL-1 interactions *per se*, but alleges that Blann, Araneo and DeFrees all teach the role of such interactions in the etiology and progression of various thrombotic conditions, including hypertension and deep vein thrombosis. The Examiner apparently contends that administration of PSGL-1 to treat conditions recited in Larsen and Cummings would also treat hypertension, and consequently thrombosis.

The Patent Office bears the burden to establish a *prima facie* case of obviousness under 35 U.S.C. § 103. *In re Fine,* 837 F.2d 1071, 1074 (Fed. Cir. 1988); *In re Deuel*, 51 F.3d 1552, 1557 (Fed. Cir. 1995). To support a rejection under § 103, the examiner must provide evidence showing "as a whole" that the legal determination sought to be proved is more probable than not. MPEP § 2142. To satisfy this burden, the Office must first demonstrate some suggestion or motivation, whether in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the prior art references, or to combine the relevant teachings from the references. *Fine,* 837 F.2d at 1074; MPEP § 2143. Next, the Office must show that one of ordinary skill in the art would have had a reasonable expectation of success on modifying the prior art references, or on combining the relevant teachings from the references. *In re Vaeck,* 947 F.2d 488, 493 (Fed. Cir. 1991). Both the suggestion or

motivation and the reasonable expectation of success *"must be founded in the prior art, not in the applicant's disclosure."* *Id.* (emphasis added). Finally, the Office must show that the combined prior art references "teach or suggest all the claim[ed] limitations." MPEP § 2143.

The Examiner bears the initial burden of providing "some suggestion of the desirability of doing what the inventor has done." MPEP § 2142. To prove that a claimed invention is, more probably than not, obvious, the cited references "must expressly or impliedly suggest the claimed invention" with all its limitations, or the examiner "must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references. " *Ex parte Clapp*, 227 U.S.P.Q. 972, 973 (Bd. Pat. App. & Inter. 1985); MPEP § 2142. Applicants respectfully submit that the Examiner has failed to meet this initial burden.

Cummings and Larsen both fail to expressly or impliedly teach or suggest using a PSGL-1 protein for treating or inhibiting thrombosis, nor do they expressly or impliedly teach or suggest that hypertension is necessarily associated with any of the conditions discussed therein. As we have discussed above, the Merck Manual does not show that hypertension is necessarily associated with atherosclerosis or stroke, nor does it always lead to thrombosis.

Neither Blann, Araneo, nor DeFrees cure the deficiencies of Cummings and Larsen. First, as discussed above, none of them teach or suggest that hypertension is necessarily associated with the conditions discussed in Cummings and/or Larsen. Second, Applicants note that each of Blann, Araneo

and DeFrees discuss compounds other than PSGL-1 and fragments thereof for treating conditions other than thrombosis in subjects having hypertension. Therefore Applicants respectfully assert that the Examiner has not demonstrated that the cited references expressly or impliedly suggest the claimed invention with all its limitations.

Applicants request that the Examiner withdraw this rejection.

B. Cummings and Larsen in view of Blann, Araneo, DeFrees, The Merck Manual, Maugeri and Johnson

Claim 27 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Cummings and Larsen, in view of Blann, Araneo, DeFrees, The Merck Manual, Maugeri, and Johnston. Claim 27 is directed to a method for inhibiting thrombus formation induced by leukotriene C_4 (LTC_4) in a subject by identifying a subject at risk of thrombosis due to hypertension and administering to the subject a composition comprising an effective amount of soluble PSGL-1 protein or a fragment thereof.

The Patent Office bears the burden to establish a *prima facie* case of obviousness under 35 U.S.C. § 103. *In re Fine,* 837 F.2d 1071, 1074 (Fed. Cir. 1988); *In re Deuel*, 51 F.3d 1552, 1557 (Fed. Cir. 1995). To support a rejection under § 103, the examiner must provide evidence showing "as a whole" that the legal determination sought to be proved is more probable than not. MPEP § 2142. To satisfy this burden, the Office must first demonstrate some suggestion or motivation, whether in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the prior art

references, or to combine the relevant teachings from the references. *Fine,* 837 F.2d at 1074; MPEP § 2143. Next, the Office must show that one of ordinary skill in the art would have had a reasonable expectation of success on modifying the prior art references, or on combining the relevant teachings from the references. *In re Vaeck,* 947 F.2d 488, 493 (Fed. Cir. 1991). Both the suggestion or motivation and the reasonable expectation of success *"must be founded in the prior art, not in the applicant's disclosure." Id.* (emphasis added). Finally, the Office must show that the combined prior art references "teach or suggest all the claim[ed] limitations." MPEP § 2143.

The Examiner bears the initial burden of providing "some suggestion of the desirability of doing what the inventor has done." MPEP § 2142. To prove that a claimed invention is, more probably than not, obvious, the cited references "must expressly or impliedly suggest the claimed invention" with all its limitations, or the examiner "must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references. " *Ex parte Clapp*, 227 U.S.P.Q. 972, 973 (Bd. Pat. App. & Inter. 1985); MPEP § 2142. Applicants respectfully submit that the Examiner has failed to meet this initial burden.

The Examiner acknowledges that Cummings and Larsen do not disclose the role of LTC_4 in thrombus formation and thrombotic conditions *per se*, but nevertheless contends that LTC_4 was a known thrombus-inducing agent associated with thrombotic conditions, as evidenced by Maugeri and Johnson. Applicants respectfully reiterate that Larsen and Cummings do not teach or

suggest treating or inhibiting thrombosis in a subject with hypertension. Neither Blann, Araneo, DeFrees, nor The Merck Manual compensate for this deficiency, as none of those references discuss administering a PSGL-1 protein or fragment thereof for treating or inhibiting thrombosis in a subject with hypertension. The addition of Maugeri and Johnson does not compensate for this deficiency, because they too fail to discuss treating or preventing thrombosis in a subject with hypertension.

Applicants respectfully assert that neither Blann, Araneo, DeFrees, The Merck Manual, Maugeri nor Johnson teach or suggest that hypertension is necessarily associated with the conditions discussed in Cummings and/or Larsen. Because the cited combination of references does not teach or suggest the claimed invention with all its limitations, Applicants respectfully submit that it does not render the claimed invention obvious. Accordingly, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants submit that this claimed invention is not anticipated or rendered obvious in view of the references cited against this application. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration and the timely allowance of the pending claims. Should the Examiner feel that this application is not in condition for allowance, Applicants request that the Examiner contact the undersigned representative at 202-408-4086.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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